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(54) Title: SOLID-PHASE NUCLEOPHILIC FLUORINATION

(57) Abstract: The present invention relates to novel solid-phase processes for the production of radiolabelled tracers, in particular for the production of ¹⁸F-labelled compounds which may be suitable for use as Positron Emission Tomography (PET) radiotracers. The invention also comprises radiopharmaceutical kits using these novel processes.

SOLID-PHASE NUCLEOPHILIC FLUORINATION

5 The present invention relates to novel solid-phase processes for the production of radiolabelled tracers, in particular for the production of ^{18}F -labelled compounds which may be suitable for use as Positron Emission Tomography (PET) radiotracers. The invention also comprises radiopharmaceutical kits using these novel processes.

10 The favoured radioisotope for PET, ^{18}F , has a relatively short half-life of 110 minutes. ^{18}F -labelled tracers for PET therefore have to be synthesised and purified as rapidly as possible, and ideally within one hour of clinical use. Standard synthetic methods for introducing fluorine-18 are relatively slow and require post-reaction purification (for example, by HPLC) which means that it is
15 difficult to obtain the ^{18}F -labelled tracer for clinical use in good radiochemical yield. There is also a need for automation to protect the operator from radiation exposure. Many radiofluorinations are complicated procedures and it is necessary to simplify them to facilitate automation.

20 The present invention provides solid-phase processes for producing ^{18}F -labelled tracers quickly and with high specific activity yet avoiding time-consuming purification steps, such that the resultant ^{18}F -labelled tracer is suitable for use in PET. The solid-phase methods also lend themselves to automation with advantages of ease of production and greater throughput. The invention also
25 comprises radiopharmaceutical kits which use such processes and thus provide the radiopharmacist or clinician with a convenient means of preparing an ^{18}F -labelled tracer.

In a general aspect, the invention provides a process for the production of an ^{18}F -
30 labelled tracer which comprises treatment of a resin-bound precursor of formula (I)

INTERNATIONAL SEARCH REPORT

Information on patent family members

ational Application No

PCT/GB 02/02505

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0010614	A	02-03-2000	AU 6239699 A EP 1105163 A1 WO 0010614 A1 US 6274119 B1 US 2002022002 A1	14-03-2000 13-06-2001 02-03-2000 14-08-2001 21-02-2002
WO 9923104	A	14-05-1999	AU 1449599 A CA 2307002 A1 EP 1027365 A2 JP 2001522034 T WO 9923104 A2 US 2002022001 A1 US 2002034473 A1	24-05-1999 14-05-1999 16-08-2000 13-11-2001 14-05-1999 21-02-2002 21-03-2002
US 5510522	A	23-04-1996	NONE	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/02505

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HARADAHIRA T ET AL: "A NEW SYNTHESIS OF 2 DEOXY-2-(18F) FLUORO-D-GALACTOSE USING (18F) FLUORIDE ION" JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS, SUSSEX, GB, vol. 25, no. 7, 1988, pages 721-729, XP000675934 ISSN: 0362-4803 scheme 1 the whole document -----	1-3,9, 13-15
A	WO 00 10614 A (PETRIC ANDREJ ;BARRIO JORGE R (US); COLE GREGORY M (US); SMALL GAR) 2 March 2000 (2000-03-02) figure 3A -----	5,11
A	WO 99 23104 A (ANDERSON LAWRENCE ;KATKI ASPANDIAR G (US); KLECKER RAYMOND W (US);) 14 May 1999 (1999-05-14) the whole document -----	4,10
A	US 5 510 522 A (SATYAMURTHY NAGICHETTIAR ET AL) 23 April 1996 (1996-04-23) the whole document -----	7

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>TOORONGIAN S A ET AL: "ROUTINE PRODUCTION OF 2-DEOXY-2-U18FFLUORO-D-GLUCOSE BY DIRECT NUCLEOPHILIC EXCHANGE ON A QUATERNARY 4-AMINOPYRIDINIUM RESIN" INTERNATIONAL JOURNAL OF RADIATION APPLICATIONS AND INSTRUMENTATION PART B: NUCLEAR MEDICINE AND BIOLOGY, ELSEVIER SCIENCE PUBLISHERS, NEW YORK, NY, US, vol. 17, no. 3, 1990, pages 273-279, XP000676335 ISSN: 0883-2897 page 278, column 2, paragraphs 2,3; figures 2,3</p> <p style="text-align: center;">--- -/-</p>	1-3,9, 13-15

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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P document published prior to the international filing date but later than the priority date claimed

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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

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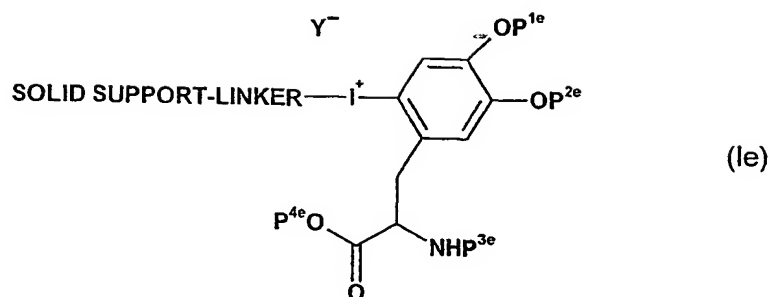
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Authorized officer

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wherein P^{1e} , P^{2e} , P^{3e} , and P^{4e} are each independently hydrogen or a protecting
 5 group and Y^- is an anion such as triflate.

13. A radiopharmaceutical kit for the preparation of an ^{18}F -labelled tracer for use
 in PET, which comprises:

- (i) a vessel containing a compound of formula (I) or (Ia), (Ib), (Ic), (Id), (Ie), or (Ih),
 10 as defined in any one of claims 1 to 7; and
- (ii) means for eluting the vessel with a source of $^{18}\text{F}^-$;
- (iii) an ion-exchange cartridge for removal of excess $^{18}\text{F}^-$; and optionally
- (iv) a cartridge for solid-phase deprotection of the resultant product of formula (II)
 or (IIa), (IIb), (IIc), (IId), (IIE), or (IIh), as defined in any one of claims 1 to 7.

15

14. A cartridge for a radiopharmaceutical kit for the preparation of an ^{18}F -labelled
 tracer for use in PET which comprises:

- (i) a vessel containing a compound of formula (I) or (Ia), (Ib), (Ic), (Id), (Ie), or (Ih),
 as defined in any one of claims 1 to 7; and
- (ii) means for eluting the vessel with a source of $^{18}\text{F}^-$.

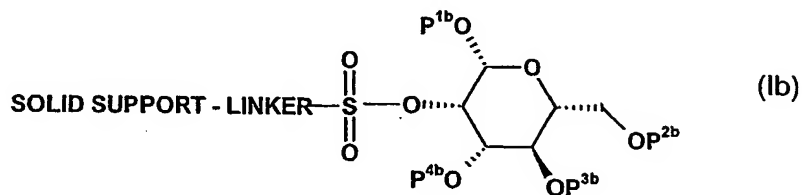
20

15. A method for obtaining a diagnostic PET image which comprises the step of
 using a radiopharmaceutical kit according to claim 13 or a cartridge for a
 radiopharmaceutical kit according to claim 14.

25

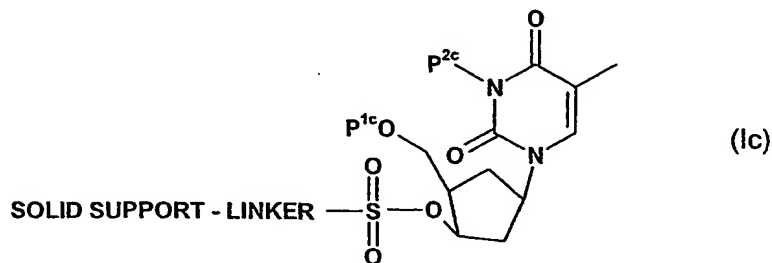
8. A process for the manufacture of a ^{18}F -labelled tracer of formula (II), according to any one of claims 1 to 7, for use in PET.

9. A compound of formula (Ib)



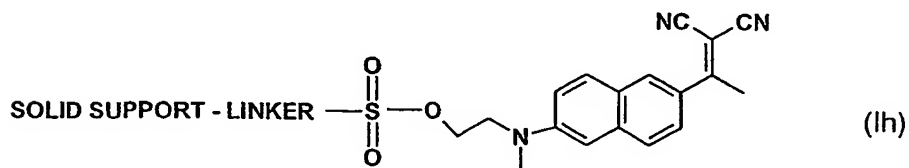
wherein P^{1b} , P^{2b} , P^{3b} , and P^{4b} are each independently hydrogen or a protecting group.

10 10. A compound of formula (Ic):

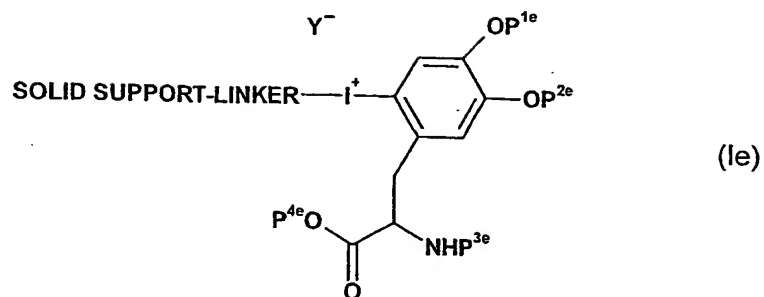


wherein P^{1c} and P^{2c} are each independently hydrogen or a protecting group.

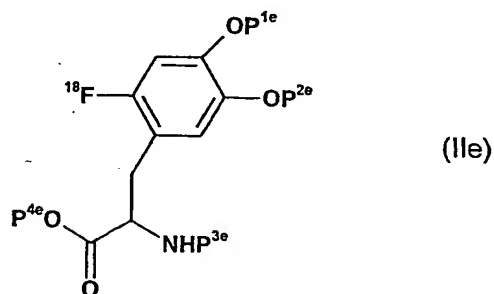
15 11. A compound of formula (Ih):



12. A compound of formula (Ie):



- 5 wherein P^{1e} , P^{2e} , P^{3e} , and P^{4e} are each independently hydrogen or a protecting group and Y^- is an anion, preferably trifluoromethylsulphonate (triflate) anion.; with $^{18}\text{F}^-$ to produce the labelled tracer of formula (IIe)



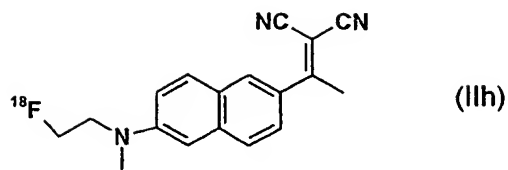
10

wherein P^{1e} , P^{2e} , P^{3e} , and P^{4e} are each independently hydrogen or a protecting group;

optionally followed by

- (i) removal of excess $^{18}\text{F}^-$, for example by ion-exchange chromatography; and/or
- 15 (ii) removal of any protecting groups; and/or
- (iii) removal of organic solvent; and/or
- (iv) formulation of the resultant compound of formula (IIe) as an aqueous solution.

20



optionally followed by

- 5 (i) removal of unreacted $^{18}\text{F}^-$, for example by ion-exchange chromatography; and/or
- (ii) removal of organic solvent; and/or
- (iii) formulation of the resultant compound of formula (IIh) as an aqueous solution.

- 10 6. A process according to claim 1 for the production of an ^{18}F -labelled tracer which comprises treatment of a solid support-bound precursor of formula (Id)

SOLID SUPPORT-LINKER- I^+ -TRACER (Id)

Y^-

15

Y^- is an anion, preferably trifluoromethylsulphonate (triflate) anion.

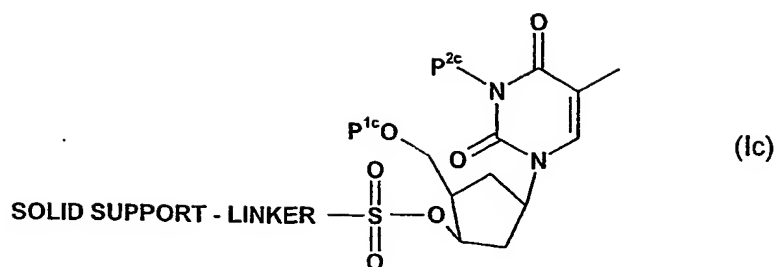
with $^{18}\text{F}^-$ to produce the labelled tracer of formula (IIId)

^{18}F -TRACER (IIId)

- 20 followed by optionally
- (i) removal of excess $^{18}\text{F}^-$, for example by ion-exchange chromatography; and/or
- (ii) removal of any protecting groups; and/or
- (iii) removal of organic solvent; and/or
- (iv) formulation of the resultant compound of formula (IIId) as an aqueous solution.

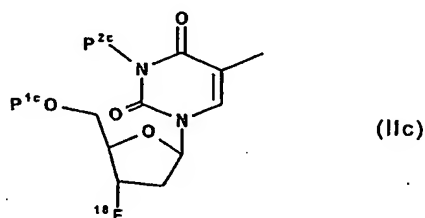
25

7. A process according to claim 1 or 6 for the production of 6-L- ^{18}F -fluorodopa (^{18}F -FDOPA) which comprises treatment of a solid support-bound precursor of formula (Ie):



wherein P^{1c} and P^{2c} are each independently hydrogen or a protecting group;

- 5 with $^{18}\text{F}^-$ to produce the labelled tracer of formula (IIc)

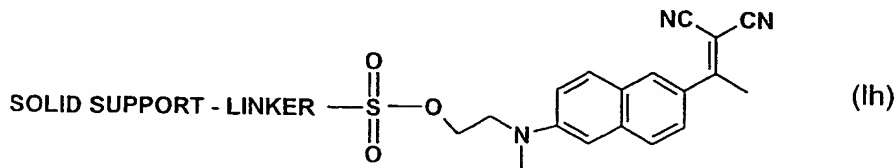


wherein P^{1c} and P^{2c} are each independently hydrogen or a protecting group;

- 10 optionally followed by
- (i) removal of excess $^{18}\text{F}^-$, for example by ion-exchange chromatography; and/or
 - (ii) removal of the protecting groups; and/or
 - (iii) removal of organic solvent; and/or
 - (iv) formulation of the resultant compound of formula (IIc) as an aqueous solution.

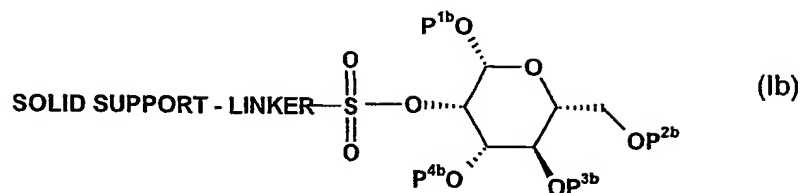
15

5. A process according to claim 1 or 2 for the production of 2-(1,1-dicyanopropen-2-yl)-6-(2-fluoroethyl)-methylamino-naphthalene (FDDNP) which comprises treatment of a solid support bound precursor of formula (Ih):

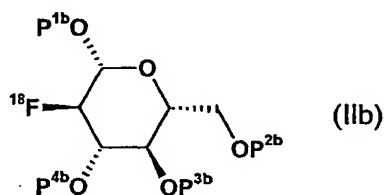


- 20 with $^{18}\text{F}^-$ to produce the labelled tracer of formula (IIh)

precursor of formula (Ib):



- 5 wherein P^{1b}, P^{2b}, P^{3b}, and P^{4b} are each independently hydrogen or a protecting group;
with ¹⁸F⁻ to produce the labelled tracer of formula (IIb)



10

wherein P^{1b}, P^{2b}, P^{3b}, and P^{4b} are each independently hydrogen or a protecting group;

optionally followed by

- (i) removal of excess ¹⁸F⁻, for example by ion-exchange chromatography; and/or
15 (ii) removal of the protecting groups; and/or
(iii) removal of organic solvent; and/or
(iv) formulation of the resultant compound of formula (IIb) as an aqueous solution.

4. A process according to claim 1 or 2 for the production of 3'-deoxy-3'-¹⁸F-fluorothymidine (¹⁸F-FLT) which comprises treatment of a solid support-bound precursor of formula (Ic):
20

Claims

1. A process for the production of an ^{18}F -labelled tracer which comprises
5 treatment of a resin-bound precursor of formula (I)

SOLID SUPPORT-LINKER-X-TRACER (I)

wherein X is a group which promotes nucleophilic substitution at a specific site on
10 the attached TRACER;

with $^{18}\text{F}^-$ to produce the labelled tracer of formula (II)

^{18}F -TRACER (II).

15

2. A process for the production of an ^{18}F -labelled tracer according to claim 1
which comprises treatment of a resin-bound precursor of formula (Ia)

SOLID SUPPORT-LINKER-SO₂-O -TRACER (Ia)

20

with $^{18}\text{F}^-$ to produce the labelled tracer of formula (II)

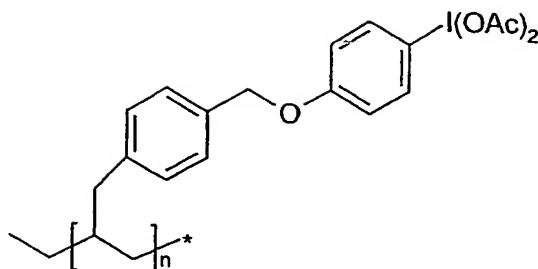
^{18}F -TRACER (II)

followed by optionally

- 25 (i) removal of excess $^{18}\text{F}^-$, for example by ion-exchange chromatography; and/or
(ii) removal of any protecting groups; and/or
(iii) removal of organic solvent; and/or
(iv) formulation of the resultant compound of formula (II) as an aqueous solution.

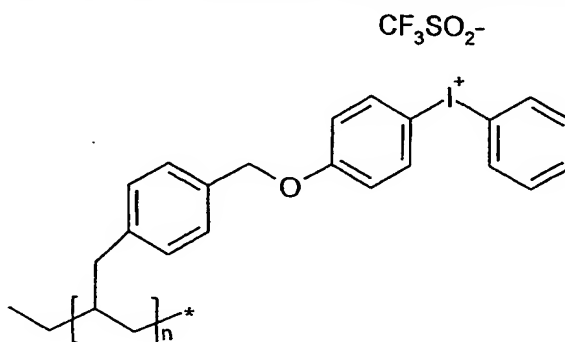
- 30 3. A process according to claim 1 or 2 for the production of 2- ^{18}F -fluoro-2-deoxy-D-glucose (^{18}F -FDG) which comprises treatment of a solid support-bound

of kryptofix, potassium carbonate and [^{18}F]-fluoride. The suspension is heated to 85°C for 10 minutes and then the solution is filtered off. The resin is washed with acetonitrile (1ml) and all the contents collected together before evaporation of the solvent prior to formulation.



A suspension of the resin above was treated with acetic anhydride and hydrogen peroxide (see method of S.Ficht, Tetrahedron, 57 (2001) 4863) in a 4:1 ratio at 40°C overnight. The resin was then filtered and washed thoroughly with methanol and then dried under high vacuum until dry.

Example 3 (iii) – Synthesis of PS (phenyl)(4-phenyl benzyl ether)iodonium triflate



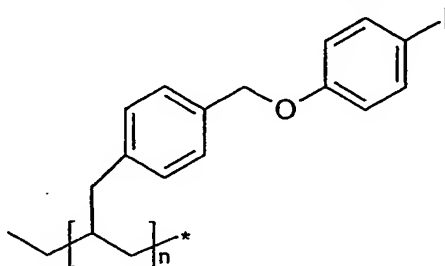
To a suspension of the resin from above in dichloromethane, trifluoromethane sulfonic acid is added dropwise at a temperature of -30°C for 15 minutes. The mixture is then warmed to 0°C for a further 15 minutes before being stirred at room temperature overnight. The suspension is then cooled to -30°C and phenyl boronic acid is added, and the suspension is stirred for 1h before warming to room temperature and further stirring overnight. The mixture is then filtered and washed thoroughly with dichloromethane and diethyl ether before drying under vacuum.

Example 3(iv) – Radiofluorination to prepare [^{18}F] fluorobenzene

To a portion of the resin held in a cartridge is added a solution in dry acetonitrile

Example 2(iii)- Radiofluorination to prepare [¹⁸F]-FDDNP

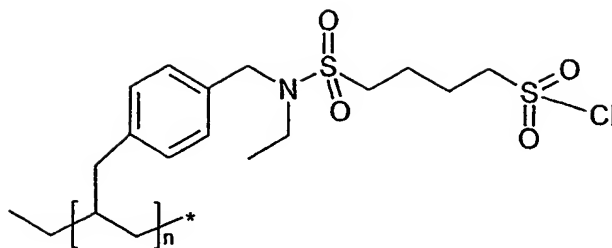
To a portion of the resin held in a cartridge is added a solution in dry acetonitrile of kryptofix, potassium carbonate and [¹⁸F]-fluoride. The suspension is heated to 85°C for 10 minutes and then the solution is filtered off. The resin is washed with acetonitrile (1ml) and all the contents collected together before evaporation of the solvent prior to formulation.

Example 3 – Synthesis of [¹⁸F]-fluorobenzeneExample 3 (i) Synthesis of PS iodo-phenyl benzyl ether

To a suspension of Wang Resin pre-swollen in DMF (2ml) a solution of cesium carbonate and iodophenol in DMF were added. The mixture was stirred for 3h at 60°C and then left at room temperature overnight. After filtration the resin was washed consecutively with methanol, dichloromethane, DMF and THF before thorough drying under high vacuum.

Example 3 (ii) Synthesis of PS diacetoxy-iodo-phenyl benzyl ether

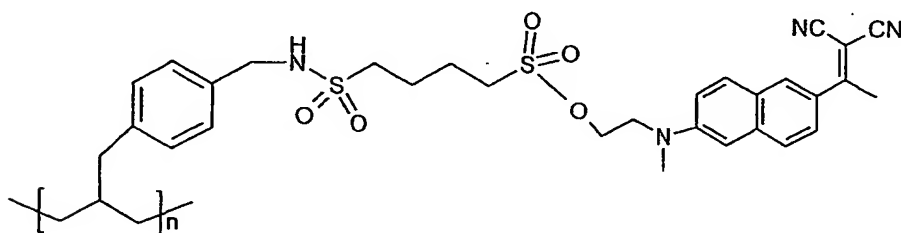
chloride



To a suspension of the resin that has been swollen in dichloromethane (5ml)
 5 excess 1,4-butane-disulfonyl chloride in dichloromethane is added together with
 an excess of triethylamine. The suspension is stirred at room temperature
 overnight. After filtration the resin is washed consecutively with dichloromethane,
 methanol, THF, water, methanol and another portion of dichloromethane. After the
 final washing the resin is dried under vacuum.

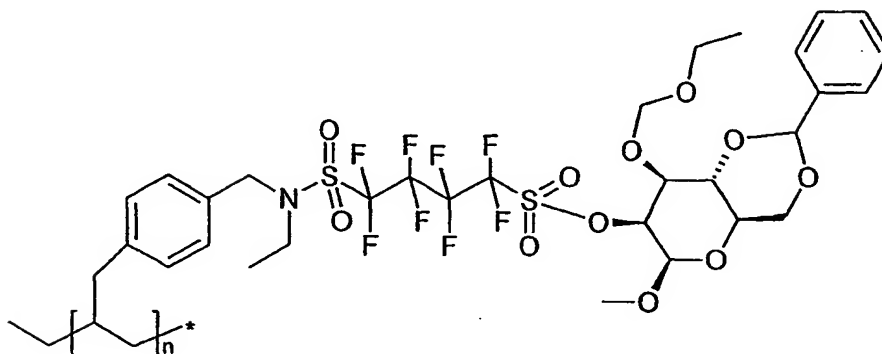
10

Example 2(ii) – Synthesis of 2-(1,1-dicyanopropen-2-yl)-6-(2-ethyl)-(methylamino)-
naphthalene resin



15

To a suspension of the resin above that has been swollen in dichloromethane (2
 ml), excess 2-(1,1-dicyanopropen-2-yl)-6-(2-hydroxyethyl)-methylamino)-
 naphthalene in dichloromethane is added together with an excess of triethylamine.
 The suspension is stirred at room temperature overnight. After filtration the resin
 20 is washed consecutively with dichloromethane and THF. After the final washing
 the resin is dried under vacuum.

Example 1(vii) Synthesis of protected mannopyranose resin

A solution of Intermediate 1 in THF was added to a portion of the resin prepared
 5 as described in Example 1(vi) above which has previously been swollen in THF. To this is added a solution of potassium *t*-butoxide in tetrahydrofuran and the suspension is stirred overnight. After filtration the resin is washed consecutively with dichloromethane and THF before drying under high vacuum.

10 Example 1(viii) Radiofluorination to prepare [¹⁸F]-FDG

To a portion of the resin (prepared as described in Example 1(vii)) held in a cartridge is added a solution in dry acetonitrile of kryptofix, potassium carbonate and [¹⁸F]-fluoride. The suspension is heated to 85°C for 10 minutes and then the
 15 solution is filtered off. The solution is then passed onto a C₁₈ solid phase extraction cartridge and washed with water to remove acetonitrile, kryptofix and potassium carbonate. Addition of more acetonitrile washes the radiofluorinated product of the cartridge into a solution of 0.1 M HCl. This solution is heated for 5 minutes before neutralization and analysis.

20

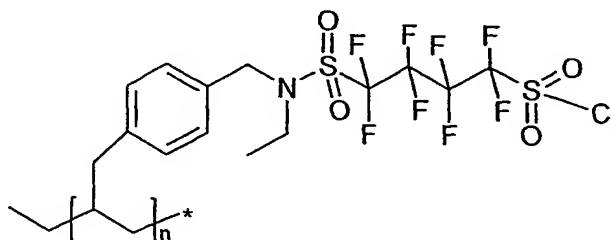
Example 2 Synthesis of 2-(1,1-dicyanopropen-2-yl)-6-(2-[¹⁸F]-fluoroethyl)-(methylamino)-naphthalene (FDDNP)

Example 2(i) – Synthesis of PS – 4-(Benzyl-ethyl-sulfonamide)-butane-1-sulfonyl

To a portion of the polystyrene resin (Novabiochem, Novasyn resin) (202mg), which had previously been swollen in dichloromethane (2ml) and then suspended in a further aliquot of dichloromethane (2ml) the perfluorobutyl-1,4-cyclic-sulfonic anhydride (116mg, 5Eq) was added. Following this di-isopropylethyl amine (0.174 ml) was added and the suspension stirred overnight at room temperature. The solvent was removed by filtration and the resin washed with consecutive addition and filtration of dichloromethane (5 ml), methanol (5ml), DMF (5ml), water (5 ml), methanol (5 ml), and dichloromethane (5ml). The resulting resin was then treated with NaOH (1M) in THF/water (2 x 2ml) before washing with consecutive portions of methanol (5ml), dichloromethane (5ml) and methanol (5 ml) again. The resin was then dried under high vacuum.

Gel Phase ^{19}F NMR (referenced to CFCl_3 , 300K) : δ -121.0, -114.8, -113.4

Example 1(vi) Synthesis of PS – 4-(Benzyl-ethyl-sulfonamide)octafluoro-butane-1-sulfonyl chloride

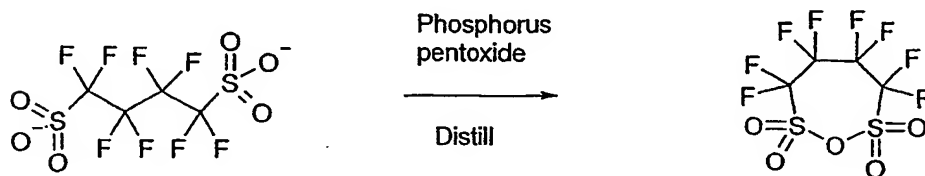


A portion of the resin prepared in the manner of Example 1(v) above is swollen with dichloromethane (2ml) and then washed consecutively with HCl (1M) in THF/water (10 x 5 ml) to give the free sulphonic acid. The resin is washed consecutively with dichloromethane, methanol and THF before drying under high vacuum.

The resin is then suspended in dichloromethane and to it is added in excess a common chlorinating agent such as phosphorous pentachloride, phosphorus trichloride or thionyl chloride. The suspension is stirred for 2 hours before filtration and then washing of the resin with dichloromethane and then THF.

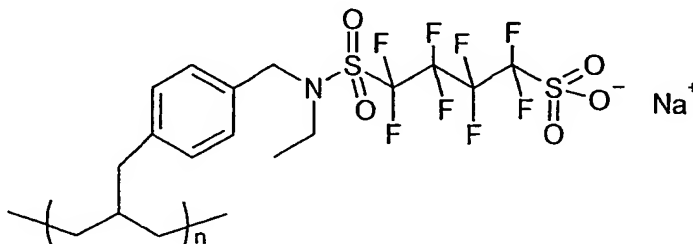
- dissolved in hot water (100ml). It was added to an ion exchange column of Amberlyst 15 resin, (40x4cm) which had been previously washed with excess 6N HCl and rinsed with distilled water. The column was then washed slowly with distilled water, and the first 300ml of aqueous solution collected. The solution was concentrated in vacuum and the residue was dried under reduced pressure at 80°C to afford perfluorobutane-1,4-bis-sulphonic acid. (11.0g, 30mmol, 88%)
- ¹H NMR (CDCl₃) δ: 8.00
- ¹⁸F NMR (CDCl₃, CFCl₃ reference) δ: -114.7, -121.3.

- 10 Example 1(iv) Preparation of perfluorobutane-1,4-bis-sulphonic acid anhydride
(Following the method described in US patent 4329,478, Fred E. Behr.)



- 15 Perfluorobutane-1,4-bis-sulphonic acid (11.0g, ~30mmol) was mixed with P₂O₅ (40g, ~10eq) and sand. The mixture was heated to 140-180°C and distilled under reduced pressure with dry-ice cooling collector to afford crude product (5.12g). Redistillation gives pure perfluorobutane-1,4-bis-sulphonic acid anhydride.
- 20 ¹⁸F NMR (CDCl₃, CFCl₃ reference) δ: -105.7, -121.8.

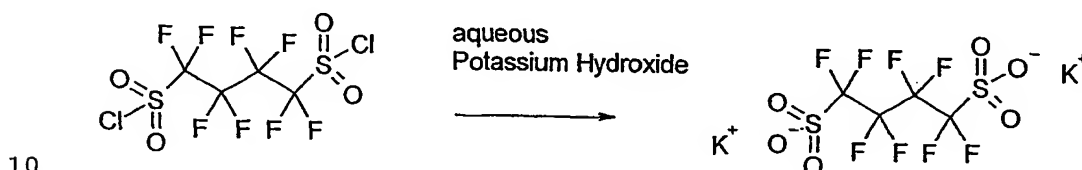
- Example 1(v) Synthesis of PS – 4-(Benzyl-ethyl-sulfonamide)octafluoro-butane-1-sulfonic acid



and the aqueous phase was extracted with CH_2Cl_2 . The combined organic phase was washed with water H_2O , brine, and dried with sodium sulphate Na_2SO_4 and concentrated to afford a waxy yellow crystalline solid. (15.4g, 74%). Recrystallization from hexane afforded off-white needles of perfluorobutane-1,4-bis-sulphonylchloride.

^{19}F NMR (CDCl_3 , CFCl_3 reference) δ : -104.4, -119.1.

Example 1(ii) Preparation of perfluorobutane-1,4-bis-sulphonate dipotassium salt

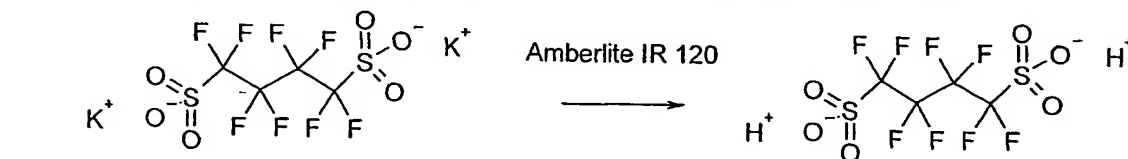


To the solution of potassium hydroxide KOH (9.8g, 5eq) in water H_2O (19ml) was added gradually perfluorobutane-1,4-bis-sulphonylchloride (14g, 35mmol) at 85°C - 90°C with stirring. After the addition, the reaction was continued for more 4 hours at the same temperature, and then it was cooled overnight. It was filtered and the solids was washed with a little of cooled water and dried in vacuum to give perfluorobutane-1,4-bis-sulphonate dipotassium salt

^{19}F NMR (CD_3OD , CFCl_3 reference) δ : -114.00, -120.11.

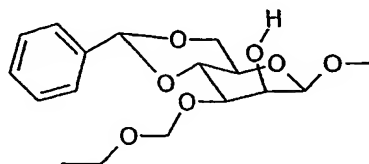
20 Example 1(iii) Preparation of perfluorobutane-1,4-bis-sulphonic acid

(Following the method described in US patent 4329,478, Fred E. Behr.)



Perfluorobutane-1,4-bis-sulphonate dipotassium salt (15g, 34.2mmol) was

Step 4 Preparation of Methyl 4,6-O- benzylidine-3-ethoxymethyl α -D-mannopyranoside

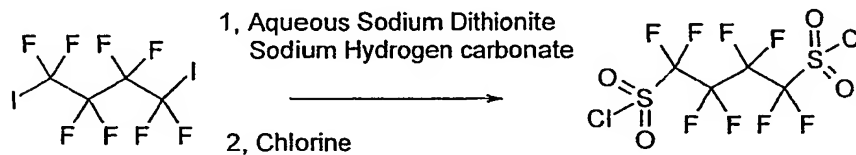


Methyl 2 keto 3-ethoxymethyl 4,6-O-benzylidine- α -D-glucopyranoside (0.5g
 5 1.3mmol) in methanol (50ml) THF (10ml) was treated with sodium borohydride
 (200mg, 5.3mmol) at room temperature with continuous stirring. The reaction was
 then concentrated in vacuum to a gum and the product partitioned between ethyl
 acetate (50ml) and 10% aqueous potassium carbonate solution (50 ml). The ethyl
 acetate solution was separated, dried over sodium sulphate and concentrated in
 10 vacuo to give methyl 3-ethoxymethyl 4,6-O- benzylidine- α -D-mannopyranoside.

Example 1(i) Preparation of perfluorobutane-1,4-bis-sulphonylchloride

(Following the method of Weiming Qiu and Donald J. Burton

15 Journal of fluorine chemistry, 60 (1993) 93-100.)



The mixture of 1,4 diiodoperfluorobutane ($I(CF_2)_4I$) (24.14g, 53.2mmol), sodium
 20 dithionite $Na_2S_2O_4$ (24g, 117.2mmol) and sodium hydrogen sulphate $NaHCO_3$
 (12.8g, 152.4mmol) in water H_2O (36ml) / Acetonitrile CH_3CN (36ml) was stirred
 at room temperature for 2 hours. It was filtered, and the filtrate was concentrated
 under reduced pressure to remove the acetonitrile. To the residue was added H_2O
 (100ml). The so obtained solution was vigorously stirred and treated with chlorine
 25 gas Cl_2 at $0^\circ C$ until the colour of I_2 disappeared. Dichloromethane CH_2Cl_2 (100ml)
 was added and the mixture vigorously shaken. The organic phase was separated,

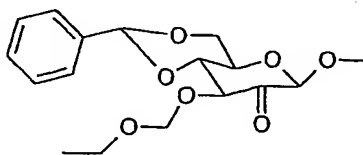
of a 40% w/v solution) in dichloromethane (150ml) was stirred vigorously with a 10% aqueous solution of sodium hydroxide (200ml) at room temperature. After 5 hours the aqueous phase was replaced with a fresh solution of 10% aqueous sodium hydroxide (200ml) to which tetrabutylammonium hydroxide (5ml of a 40% w/v solution) was added, and rapid stirring continued overnight. The organic phase was then separated dried over sodium sulphate and evaporated in vacuum. Thin layer chromatography of the residue (40-60 hexanes-ethyl acetate 2:1) on silica developed by spraying with ceric ammonium molybdate (see above) indicated the presence of three new alkylated products. Chromatography on silica (1kg, dry weight) in a gradient of 40-60 hexanes-ethyl acetate 2:1 to 1:1 gave three fractions which NMR indicated to be

Fraction 1: Methyl-2,3, - diethoxymethyl 4,6-O- benzylidine- α -D-glucopyranoside

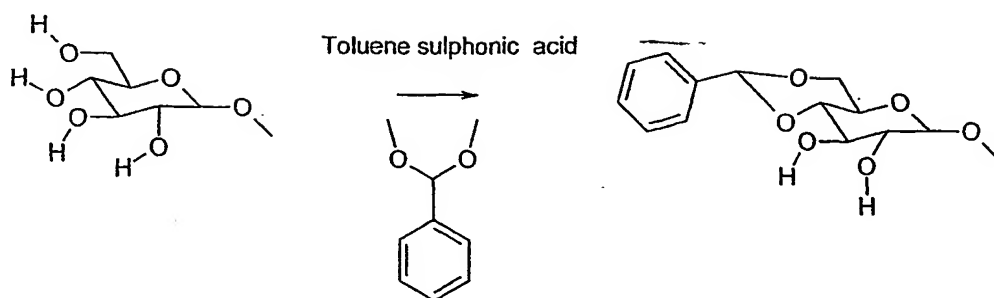
Fraction 2: Methyl-2- ethoxymethyl 4,6-O- benzylidine- α -D-glucopyranoside

Fraction 3: Methyl 3- ethoxymethyl 4,6-O- benzylidine- α -D-glucopyranoside

Step 3 Preparation of Methyl 2 keto 3-ethoxymethyl 4,6-O- benzylidine- α -D-glucopyranoside



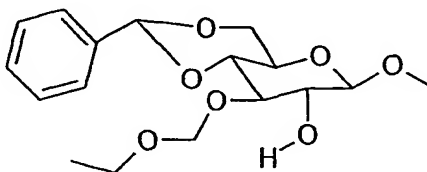
Methyl 4,6-O- benzylidine-3- ethoxymethyl α -D-glucopyranoside (3g, 8.0mmol) was treated with methylsulfoxide (50ml) and acetic anhydride (25ml) at room temperature for 24 h until the reaction will be adjudged completed by tlc (Petrol ether/ Ethyl acetate 1:1). developed with cerium ammonium molybdate. The solution was then diluted with diethyl ether (200ml) and washed with 10% aqueous potassium carbonate solution to hydrolyse the excess acetic anhydride. The ether layer was separated and washed with water (100ml). The ether layer was separated, dried over sodium sulphate and concentrated in vacuum to give a crystalline solid. Recrystallization from ether/petrol gave 1.5 g of Methyl 2 keto-3-ethoxymethyl 4,6-O- benzylidine- α -D-glucopyranoside.



Following literature Evans, M. E. Carbohydrate Research (1972), 21(3), 473-5, Methyl- α -D-glucopyranoside (Aldrich, 257mmol) in DMF (200ml) was treated with
 5 α,α -dimethoxy toluene 39.0 g 257mmol) and toluene sulphonic acid monohydrate 100mg in a 1l round bottomed flask. This was attached to a Buchi and evacuated and rotated. The flask was lowered into a water bath at 65°C and the DMF allowed to gently reflux into the vapour duct but not to distil out. The temperature of the water bath was then raised to 100 °C and the DMF distilled from the
 10 reaction. When the distillation of the reaction was complete the reaction was cooled and treated with a solution of sodium hydrogen carbonate (5g) in water (750ml) and ethyl alcohol (250ml). The reaction was heated to 95°C on a water bath and stirred until the product became finely dispersed. The reaction was then cooled to 4°C and the product filtered off washed well with water and dried in
 15 vacuum.

m.p. 207-208.5

20 Step 2 Preparation of Methyl 4,6-O- benzylidine-3- ethoxymethyl- α -D-glucopyranoside



Methyl-4,6-O-benzylidine- α -D-glucopyranoside, (19.2g, 68mmole), ethoxymethylchloride (9.7g, 81.6mmol) and tetrabutylammonium hydroxide (5ml

The invention further provides a cartridge for a radiopharmaceutical kit for the preparation of an ^{18}F -labelled tracer for use in PET which comprises:

- (i) a vessel containing a compound of formula (I) or (Ia to Ih); and
- (ii) means for eluting the vessel with a source of $^{18}\text{F}^-$.

5

In a further aspect of the invention, there is provided a method for obtaining a diagnostic PET image which comprises the step of using a radiopharmaceutical kit or a cartridge for a radiopharmaceutical kit as described above.

10 The invention will now be illustrated by way of the following Examples.

Throughout the Examples, abbreviations used are as follows:

DMF: N,N-dimethylformamide

w/v : weight/volume

h : hour(s)

15 tlc : thin layer chromatography

THF : tetrahydrofuran

eq. : equivalents

Examples

20

Example 1. Synthesis of 2[^{18}F]-fluoro-2-deoxy-D-glucose (FDG)

Intermediate 1

Preparation of Methyl -4,6-O- benzylidene-3-ethoxy methyl α -D-mannopyranoside

25

Step 1: Synthesis of Methyl 4,6-O- benzylidene- α -D-glucopyranoside

present invention.

As described above, the advantages of such solid-phase processes for preparation of ^{18}F -labelled tracers include the relative speed of the process, simplified purification methods and ease of automation- all of which mean that the processes are suitable for preparation of ^{18}F -labelled tracers for use in PET. Accordingly, the present invention provides the use of a process for the manufacture of a ^{18}F -labelled tracer of formula (II) or (IIa to IIh) for use in PET.

Conveniently, the solid support bound precursor of formula (I) could be provided as part of a kit to a radiopharmacy. The kit may contain a cartridge which can be plugged into a suitably adapted automated synthesiser. The cartridge may contain, apart from the solid support-bound precursor, a column to remove unwanted fluoride ion, and an appropriate vessel connected so as to allow the reaction mixture to be evaporated and allow the product to be formulated as required. The reagents and solvents and other consumables required for the synthesis may also be included together with a compact disc carrying the software which allows the synthesiser to be operated in a way so as to meet the customers requirements for radioactive concentration, volumes, time of delivery etc.

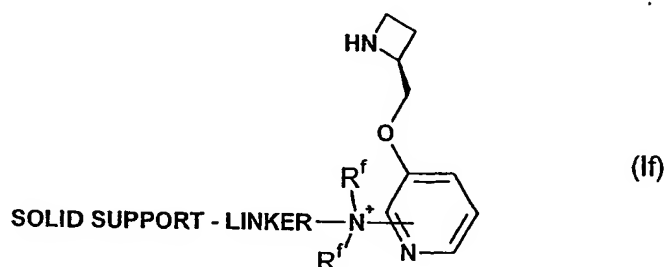
Conveniently, all components of the kit are disposable to minimise the possibilities of contamination between runs and may be sterile and quality assured.

The invention further provides a radiopharmaceutical kit for the preparation of an ^{18}F -labelled tracer for use in PET, which comprises:

- (i) a vessel containing a compound of formula (I) or (Ia to Ih); and
- (ii) means for eluting the vessel with a source of $^{18}\text{F}^-$;
- (iii) an ion-exchange cartridge for removal of excess $^{18}\text{F}^-$; and optionally
- (iv) a cartridge for solid-phase deprotection of the resultant product of formula (II) or (IIa to IIh).

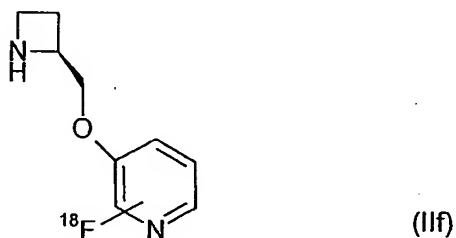
The present invention provides in a further aspect, a process for the production of 2-, 5- or 6-fluoro-3-(2(s)-azetidylmethoxy)pyridines which comprises treatment of a solid support-bound precursor of formula (If):

5



wherein the groups R^f are each independently selected from C_{1-6} alkyl; with $^{18}F^-$ to produce the labelled tracer of formula (IIf)

10



optionally followed by

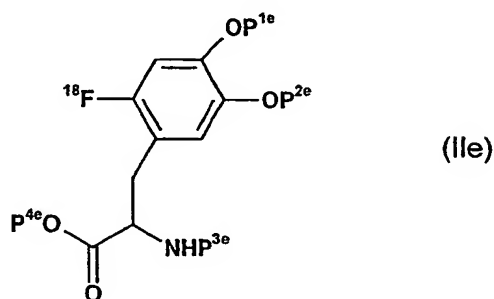
- 15 (i) removal of excess $^{18}F^-$, for example by ion-exchange chromatography; and/or
 (ii) removal of organic solvent; and/or
 (iii) formulation of the resultant compound of formula (IIf) as an aqueous solution.

20 Some of the compounds of formula (I) are novel and thus form a further aspect of the present invention. Thus, for example, compounds of formula (Ia), in particular those of formula (Ib), (Ic), (Ig) and (Ih), and compounds of formula (Id), in particular those of formula (Ie) all as defined above, form separate aspects of the

wherein P^{1e} , P^{2e} , P^{3e} , and P^{4e} are each independently hydrogen or a protecting group and Y^- is an anion such as triflate;

with $^{18}F^-$ to produce the labelled tracer of formula (IIe)

5



wherein P^{1e} , P^{2e} , P^{3e} , and P^{4e} are each independently hydrogen or a protecting group;

10 optionally followed by

- (i) removal of excess $^{18}F^-$, for example by ion-exchange chromatography; and/or
- (ii) removal of any protecting groups; and/or
- (iii) removal of organic solvent; and/or
- (iv) formulation of the resultant compound of formula (IIe) as an aqueous solution.

15

In this aspect of the invention, the hydroxyl, amine, and acid functionality of the DOPA starting material are conveniently protected as esters, suitably C_{1-6} alkyl esters, preferably as acyl esters such as t-butoxycarbonyl, or ethers, preferably as C_{1-6} alkyl ethers, or amides. These protecting groups may be conveniently

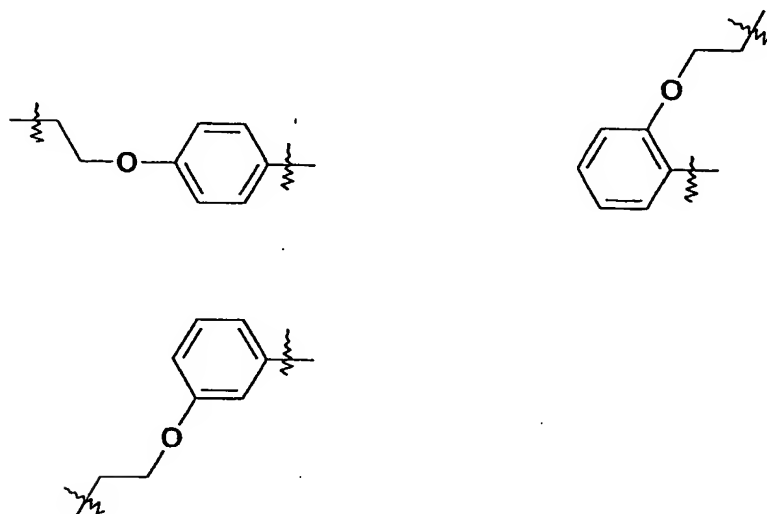
20 removed by hydrolysis, for example in the presence of acid or base. Such deprotection may be effected using a solid supported acid or base catalysts that render the need for post deprotection neutralisation unnecessary.

In the compounds of formula (Ie), preferred LINKER groups are as described for

25 the compounds of formula (Id) and the SOLID SUPPORT is suitably a polystyrene resin.

compound of formula (Id) may be separated by filtration and washing with an inert solvent.

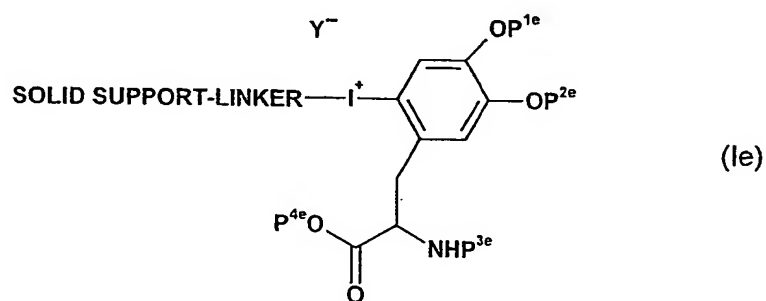
In the compound of formula (Id), the LINKER is as defined above but comprises
 5 an aryl group (suitably phenyl) adjacent to the I⁺. Preferred examples include



In the compound of formula (Id), Y⁻ is an anion, preferably trifluoromethylsulphonate (triflate) anion.

10

The present invention provides in a further aspect, a process for the production of 6-L-¹⁸F-fluorodopa (¹⁸F-FDOPA) which comprises treatment of a solid support-bound precursor of formula (Ie):



15

with $^{18}\text{F}^-$ to produce the labelled tracer of formula (IId)

5 ^{18}F -TRACER (IId)

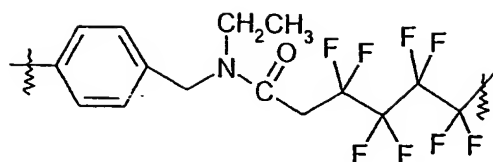
followed by optionally

- (i) removal of excess $^{18}\text{F}^-$, for example by ion-exchange chromatography; and/or
- (ii) removal of any protecting groups; and/or
- (iii) removal of organic solvent; and/or
- 10 (iv) formulation of the resultant compound of formula (IId) as an aqueous solution.

In the compound of formula (Id), the tracer is suitably an aryl containing compound such as a phenyl containing compound, preferably a substituted phenyl ring. In one such preferred aspect, the tracer prepared is FDOPA.

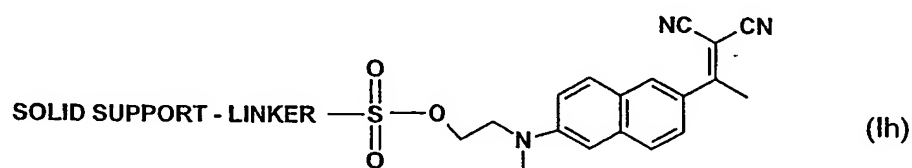
15

The compound of formula (Id) may be conveniently prepared from a functionalised commercially available resin such as a Merrifield Resin or Wang Resin. Suitably, a hydroxyiodoaryl (such as an iodophenol) containing LINKER group is treated with an inorganic base, such as cesium carbonate and then added to the resin, 20 pre-swollen with an inert solvent, such as N,N-dimethylformamide and allowed to react at elevated temperature, for example 30 to 80°C. Excess reagents may be removed by washing the resin with further inert solvent. The resultant iodophenol functionalised resin may then be treated with a source of acetate anions (such as acetic acid, acetic anhydride, or acetyl chloride) in the presence of an oxidising 25 agent, such as hydrogen peroxide to provide the corresponding diacetoxy-iodophenyl functionalised resin. The diacetoxy-iodophenyl functionalised resin may then be stirred in an inert solvent, such as dichloromethane, in the presence of acid such as hydrochloric acid, trifluoromethane sulphonic acid, or acetic acid at a low temperature, suitably -40°C to 10°C before addition of the tracer, suitably 30 functionalised as a boronic acid or trialkyl tin derivative which may be coupled to the resin at a non-extreme temperature. As in previous steps, the desired

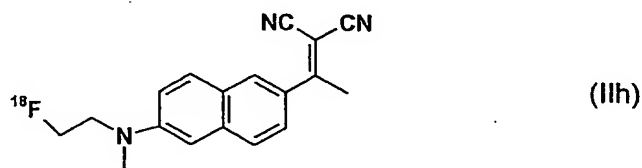


and the solid support is suitably a polystyrene resin.

The present invention provides in a further aspect, a process for the production of 2-(1,1-dicyanopropen-2-yl)-6-(2-fluoroethyl)-methylamino)-naphthalene (FDDNP) which comprises treatment of a solid support bound precursor of formula (Ih):



with $^{18}\text{F}^-$ to produce the labelled tracer of formula (IIh)



10

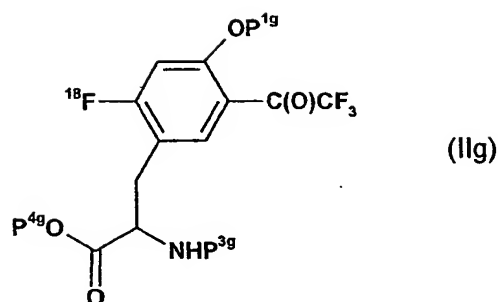
optionally followed by

- (i) removal of unreacted $^{18}\text{F}^-$, for example by ion-exchange chromatography;
- and/or
- (ii) removal of organic solvent; and/or
- (iii) formulation of the resultant compound of formula (IIh) as an aqueous solution.

In a further aspect, the invention provides a process for the production of an ^{18}F -labelled tracer which comprises treatment of a solid support-bound precursor of formula (Id)



Y⁻



wherein P^{19} , P^{39} , and P^{49} are each independently hydrogen or a protecting group such as t-butoxycarbonyl;

optionally followed by

- 5 (i) removal of excess $^{18}\text{F}^-$, for example by ion-exchange chromatography; and/or
- (ii) conversion of the $-\text{C}(\text{O})\text{CF}_3$ group to a hydroxyl group; and/or
- (iii) removal of any protecting groups; and/or
- (iv) removal of organic solvent; and/or
- (v) formulation of the resultant FDOPA as an aqueous solution.

10

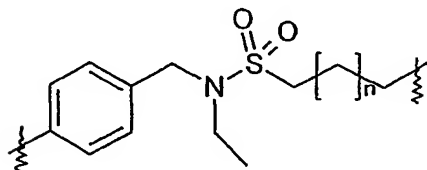
In this aspect of the invention, the hydroxyl functionality of the DOPA starting material are conveniently protected as esters, suitably C_{1-6} alkanoic esters, preferably as acetate esters, or carbonate esters such as t-butoxycarbonyl esters.

- 15 The acid functionality may be protected as a C_{1-6} alkyl ester, preferably ethyl ester and the amine functionality may be protected as an amide preferably formyl or as a urethane, preferably as t-butoxycarbonyl urethane. Ester formyl and urethane protecting groups may be conveniently removed by hydrolysis, for example in the presence of acid or base. Such deprotection may be effected using a solid supported acid or base catalysts that render the need for post deprotection
- 20 neutralisation unnecessary. Conversion of the $-\text{C}(\text{O})\text{CF}_3$ group to a hydroxyl group, may be effected by treatment with an oxidising agent such as meta-chloro perbenzoic acid, followed by mild acidic hydrolysis. In this aspect of the invention, a particularly suitable LINKER is

above. Suitably, the amine and hydroxyl groups are protected as esters, suitably C_{1-6} alkyl esters, preferably as acyl esters. Ester protecting groups may be conveniently removed by hydrolysis, for example in the presence of acid or base.

Such deprotection may be effected using a solid supported acid or base catalyst
 5 that renders the need for post deprotection neutralisation unnecessary

In the compound of (Ic), the Linker is preferably:

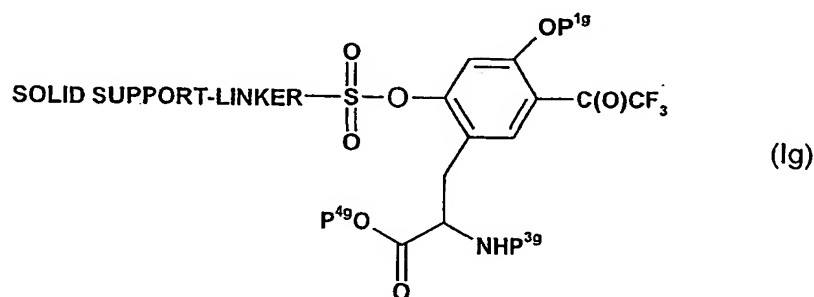


wherein n is 0 to 3.

10

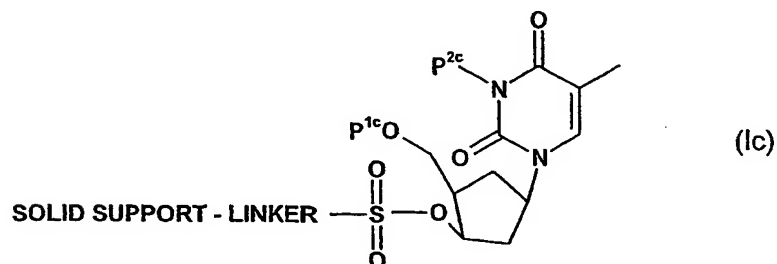
In a further aspect of the invention, the TRACER in the compound of formula (Ia) may be a peptide or protein such as a peptide comprising from 2 to 1,000 amino acids.

15 In a further aspect of the invention, there is provided a process for the production of 6-L- ^{18}F -fluorodopa (^{18}F -FDOPA) which comprises treatment of a solid support-bound precursor of formula (Ig):



20 wherein P^{19} , P^{39} , and P^{49} are each independently hydrogen or a protecting group such as t-butoxycarbonyl;
 with $^{18}F^-$ to produce the labelled tracer of formula (IIg)

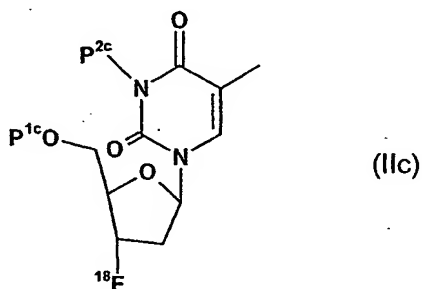
The present invention provides in a further aspect, a process for the production of 3'-deoxy-3'- ^{18}F -fluorothymidine (^{18}F -FLT) which comprises treatment of a solid support-bound precursor of formula (Ic):



wherein P^{1c} and P^{2c} are each independently hydrogen or a protecting group;

with $^{18}\text{F}^-$ to produce the labelled tracer of formula (IIc)

10



wherein P^{1c} and P^{2c} are each independently hydrogen or a protecting group;

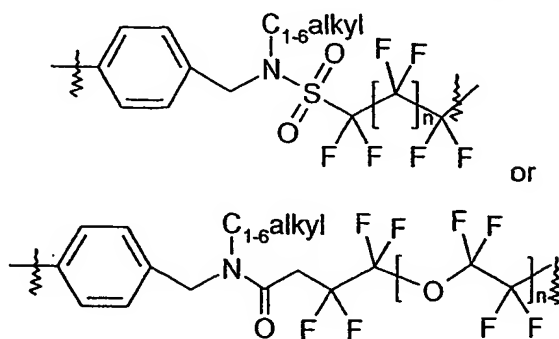
optionally followed by

- 15
- (i) removal of excess $^{18}\text{F}^-$, for example by ion-exchange chromatography; and/or
 - (ii) removal of the protecting groups; and/or
 - (ii) removal of organic solvent; and/or
 - (iii) formulation of the resultant compound of formula (IIc) as an aqueous solution.

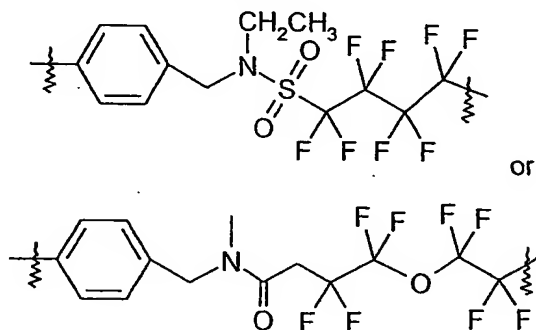
20 In this aspect of the invention, the amine and hydroxyl functional groups in the thymidine precursor are suitably protected using standard methods as referred to

- (ii) removal of the protecting groups; and/or
- (iii) removal of organic solvent; and/or
- (iv) formulation of the resultant compound of formula (IIb) as an aqueous solution.

5 In the compound of formula (Ib) the LINKER is preferably



wherein n is 0 to 3, and is more preferably



10

and the SOLID SUPPORT is suitably a polystyrene resin.

Removal of any protecting groups from the compound of formula (IIb) may be effected by standard methods as referred to above. In a preferred embodiment of this aspect of the invention, the sugar hydroxyl groups are protected as esters, suitably C₁₋₆ alkanolic esters, preferably as acetate esters, or as ethers, preferably C₁₋₆ alkoxy methyl ethers, or acetals. Ester, acetal, or ether protecting groups may be conveniently removed by hydrolysis, for example in the presence of acid or base. Such deprotection may be effected on using solid supported acid or base catalysts that render the need for post deprotection neutralisation unnecessary

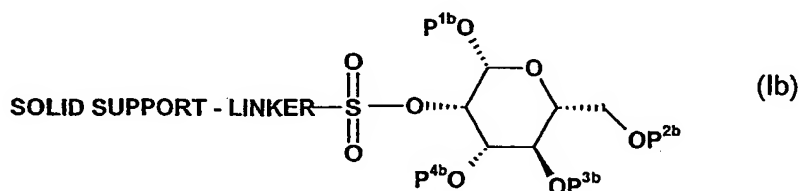
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evaporation at elevated temperature *in vacuo* or by passing a stream of inert gas such as nitrogen or argon over the solution.

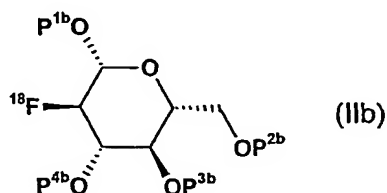
Before use of the ^{18}F -labelled tracer, it may be appropriate to formulate it, for example as an aqueous solution by dissolving the ^{18}F -labelled tracer in sterile isotonic saline which may contain up to 10% of a suitable organic solvent such as ethanol, or a suitable buffered solution such as phosphate buffer. Other additives may be added such as ascorbic acid to reduce radiolysis.

The present invention provides, in a further aspect, a process for the production of 2- ^{18}F -fluoro-2-deoxy-D-glucose (^{18}F -FDG) which comprises treatment of a solid support-bound precursor of formula (Ib):



wherein P^{1b} , P^{2b} , P^{3b} , and P^{4b} are each independently hydrogen or a protecting group;

with $^{18}\text{F}^-$ to produce the labelled tracer of formula (IIb)



wherein P^{1b} , P^{2b} , P^{3b} , and P^{4b} are each independently hydrogen or a protecting group;

optionally followed by

(i) removal of excess $^{18}\text{F}^-$, for example by ion-exchange chromatography; and/or

As would be apparent to the person skilled in the art, it may be necessary to protect functional groups in the TRACER to avoid unwanted reactions during the radiolabelling process. Such protection may be achieved using standard methods of protecting group chemistry. After the radiolabelling is complete, any protecting groups may be removed by simple procedures which are also standard in the art.

Suitable protection and deprotection methodologies may be found, for example, in *Protecting Groups in Organic Synthesis*, Theodora W. Greene and Peter G. M. Wuts, published by John Wiley & Sons Inc.

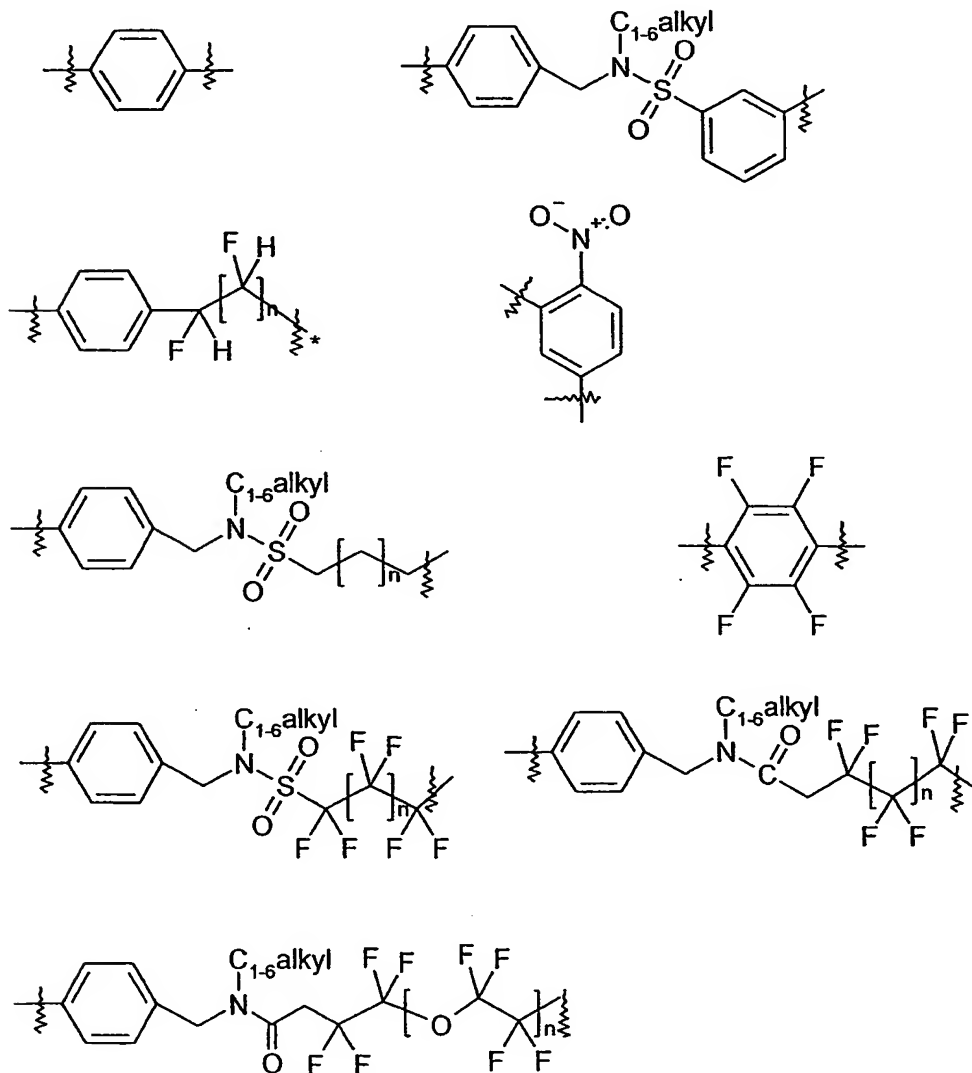
10 Treatment of the compound of formula (I) or (Ia) with $^{18}\text{F}^-$ may be effected by treatment with any suitable source of $^{18}\text{F}^-$, such as Na^{18}F , K^{18}F , Cs^{18}F , tetraalkylammonium ^{18}F fluoride, or tetraalkylphosphonium ^{18}F fluoride. To increase the reactivity of the fluoride, a phase transfer catalyst such as 4,7,13,16,21,24 hexaoxa-1,10-diazabicyclo[8,8,8] hexacosane may be added and
15 the reaction performed in a non protic solvent. These conditions give reactive fluoride ions. The treatment with $^{18}\text{F}^-$ is suitably effected in the presence of a suitable organic solvent such as acetonitrile, dimethylformamide, dimethylsulphoxide, tetrahydrofuran, dioxan, 1,2 dimethoxyethane, sulfolane, N-methylpyrrolidine, at a non-extreme temperature, for example, 15°C to
20 180°C , preferably at elevated temperature. On completion of the reaction, the ^{18}F -labelled tracer of formula (II) dissolved in the solvent is conveniently separated from the solid-phase by filtration. The same fluorination techniques may be used in the following more specific aspects of the invention.

25 Any excess $^{18}\text{F}^-$ may be removed from the solution of ^{18}F -tracer by any suitable means, for example by ion-exchange chromatography or solid phase absorbents. Suitable ion-exchange resins include BIO-RAD AG 1-X8 or Waters QMA and suitable solid phase absorbents include alumina. The excess $^{18}\text{F}^-$ may be removed using such solid phases at room temperature in aprotic solvents.

30

Any organic solvent may be removed by any standard method such as by

- serves to space the reactive site sufficiently from the solid support structure so as to maximise reactivity. Suitably, the LINKER comprises zero to four aryl groups (suitably phenyl) and/or a C₁₋₆ alkyl or C₁₋₆ haloalkyl (suitably C₁₋₆ fluoroalkyl), and optionally one to four additional functional groups such as amide or sulphonamide groups. Examples of such linkers are well known to those skilled in the art of solid-phase chemistry, but include:

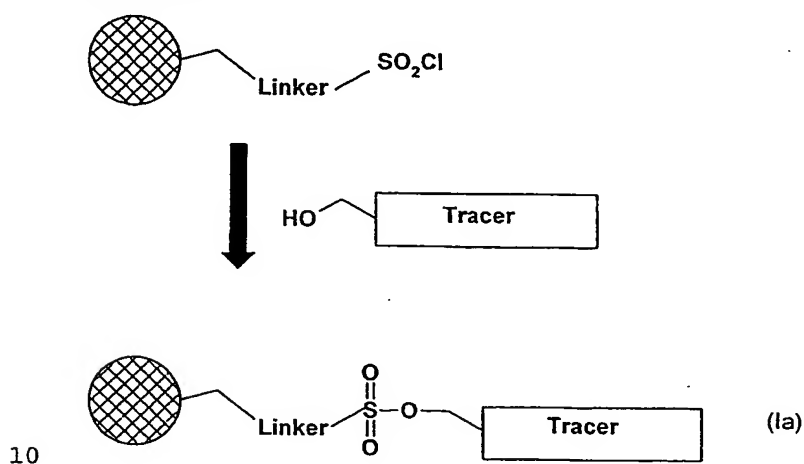


10

wherein at each occurrence, n is an integer of 0 to 3.

containing a non-nucleophilic soluble base such as sodium hydride or a trialkylamine, for example triethylamine or diisopropylethylamine. The reaction may be carried out at a temperature of 10 to 80°C, optimally at ambient temperature for a period of from around 1 to 24 hours. The excess alcohol and base may then be removed from the solid support by washing with further portions of an inert solvent such as chloroform, dichloromethane, or tetrahydrofuran.

Scheme 1



In the compounds of formulae (I) and (Ia) and in the following more specific aspects of the invention, the "SOLID SUPPORT" may be any suitable solid-phase support which is insoluble in any solvents to be used in the process but to which the LINKER and/or TRACER can be covalently bound. Examples of suitable SOLID SUPPORT include polymers such as polystyrene (which may be block grafted, for example with polyethylene glycol), polyacrylamide, or polypropylene or glass or silicon coated with such a polymer. The solid support may be in the form of small discrete particles such as beads or pins, or as a coating on the inner surface of a cartridge or on a microfabricated vessel.

In the compounds of formulae (I) and (Ia) and in the following more specific aspects of the invention, the "LINKER" may be any suitable organic group which

SOLID SUPPORT-LINKER-SO₂-O -TRACER (Ia)

with ¹⁸F⁻ to produce the labelled tracer of formula (II)

5

¹⁸F-TRACER (II)

followed by optionally

- (i) removal of excess ¹⁸F⁻, for example by ion-exchange chromatography; and/or
- (ii) removal of any protecting groups; and/or
- 10 (iii) removal of organic solvent; and/or
- (iv) formulation of the resultant compound of formula (II) as an aqueous solution.

In the compound of formula (Ia), the TRACER is suitably FDG, FLT, FDDNP or a precursor thereof in which one or more functional groups have been protected, or
15 an activated precursor of FDOPA. Most suitably, the TRACER in the compound of formula (Ia) is FDG or a precursor thereof.

As shown in Scheme 1, the compound of formula (Ia) may be conveniently prepared from any sulphonic acid functionalised commercially available resin,
20 such as Merrifield Resin, NovaSyn® TG Bromo Resin, (Bromomethyl)phenoxymethyl polystyrene, or Wang Resin which may be reacted with a chlorinating agent to give the corresponding sulphonyl chloride resin. This may be carried out by treating the resin with, for example, phosphorus pentachloride, phosphorus trichloride, oxalyl chloride, or thionyl chloride, in an
25 appropriate inert solvent such as dichloromethane, chloroform, or acetonitrile, and heating at elevated temperature for a period of time. The excess reagent may then be removed from the resin by washing with further portions of the inert solvent. The sulphonyl chloride resin may then be reacted with the alcohol analogue of the tracer to produce the resin-bound precursor of formula (Ia). This
30 may be carried out by treating the resin with a solution of the alcohol in an inert solvent such as chloroform, dichloromethane, acetonitrile, or tetrahydrofuran

SOLID SUPPORT-LINKER- X -TRACER (I)

with $^{18}\text{F}^-$ to produce the labelled tracer of formula (II)

5

^{18}F -TRACER (II)

As the ^{18}F -labelled tracer of formula (II) is removed from the solid-phase into solution, all unreacted precursor remains bound to the resin and can be
10 separated by simple filtration, thus obviating the need for complicated purification, for example by HPLC. The ^{18}F -labelled tracer of formula (II) may be cleaned up by removal of excess F^- , for example by ion-exchange chromatography and/or by removal of any organic solvent. The resultant ^{18}F -labelled tracer of formula (II) may then be further made-up into an aqueous formulation for clinical use.

15

Examples of tracers which may be ^{18}F -labelled in the manner of the invention include 2-fluoro-2-deoxy-D-glucose (FDG), 6-fluoro-L-DOPA (FDOPA), 3'-deoxy-3'-fluorothymidine (FLT), 2-(1,1-dicyanopropen-2-yl)-6-(2-fluoroethyl)-methylamino)-naphthalene (FDDNP), 2-, 5-, and 6-fluoro (2(S)-
20 azetynylmethoxy)pyridines, N-succinimidyl-4-[^{18}F]fluorobenzoate ([^{18}F]-SFB) and peptides. In preferred aspects of the invention, the tracer produced is selected from FDG, FDOPA, FLT, and FDDNP, and is most preferably FDG or FDOPA.

In the compounds of formula (I), X is a group which promotes nucleophilic
25 substitution at a specific site on the attached TRACER. Examples of X include $-\text{SO}_2\text{O}-$ as in formula (Ia) below, I^+ as in formula (Id) below, or $-\text{N}(\text{C}_{1-6}\text{alkyl})_2^+$ as in formula (If) below.

In a further aspect, the invention provides a process for the production of an ^{18}F -
30 labelled tracer which comprises treatment of a resin-bound precursor of formula (Ia)

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